been demonstrated in dogs under laboratory conditions. The precise mechanism by which methylene blue produces the characteristic erythrocytic inclusion bodies (Heinz bodies) and associated hemolytic anemia is unclear.

(2) The effectiveness of orally administered methylene blue as a urinary antiseptic is open to question. It appears that following oral administration, methylene blue is poorly and erratically absorbed and also slowly and erratically excreted in the urine. Studies in the dog indicate it is excreted in the urine essentially as leukomethylene blue stabilized in some manner. Methylene blue itself is stepwise demethylated in alkaline solutions (alkaline urine being a frequent consequence of urinary infection) to Azure B, Azure A, and Azure C. The antiseptic efficacy of all of these excretion products is unsubstantiated.

(3) In view of the foregoing, the Commissioner has concluded that animal drugs containing methylene blue for oral use in cats or dogs are neither safe nor generally recognized as effective within the meaning of section 201(v) of the act and are therefore considered new animal drugs. Accordingly, all prior formal and informal opinions expressed by the Food and Drug Administration that such drugs are ''not new drugs'' or ''no longer new drugs'' are hereby revoked.

(b) Animal drugs that contain methylene blue for oral use in cats or dogs and not the subject of an approved new animal drug application (NADA) are deemed to be adulterated under the provisions of section 501(a) (5) and/or (6) and/or misbranded under section 502(a) of the act and subject to regulatory action as of April 10, 1978.

(c) Sponsors of animal drugs that contain methylene blue for oral use in cats or dogs and not the subject of an approved new animal drug application (NADA) may submit an application in conformity with § 514.1 of this chapter. Such applications will be processed in accordance with section 512 of the act. Submission of an NADA will not constitute grounds for continued marketing of this drug substance until such application is approved.

(d) New animal drug applications required by this regulation pursuant to section 512 of the act shall be submitted to the Food and Drug Administration. Center for Veterinary Medicine, Office of New Animal Drug Evaluation (HFV-100), 7500 Standish Pl., Rockville, MD 20855.

[43 FR 9803, Mar. 10, 1978; 43 FR 12310, Mar. 24, 1978, as amended at 54 FR 18279, Apr. 28, 1989; 57 FR 6475, Feb. 25, 1992; 60 FR 38480, July 27, 1995]

§ 500.29 Gentian violet for use in animal feed.

The Food and Drug Administration has determined that gentian violet is not generally recognized as safe for use in animal feed and is a food additive subject to section 409 of the Federal Food, Drug, and Cosmetic Act (the act), unless it is intended for use as a new animal drug, in which case it is subject to section 512 of the act. The Food and Drug Administration has determined that gentian violet is not prior sanctioned for any use in animal feed.

[56 FR 40506, Aug. 15, 1991]

§ 500.30 Gentian violet for animal drug use.

The Food and Drug Administration (FDA) has determined that gentian violet is not generally recognized as safe and effective for any veterinary drug use in food animals and is a new animal drug subject to section 512 of the Federal Food, Drug, and Cosmetic Act. FDA has determined that gentian violet is not exempted from new animal drug status under the ''grandfather'' provisions of the Drug Amendments of 1962 (21 U.S.C. 342).

[56 FR 40507, Aug. 15, 1991]

§ 500.45 Use of polychlorinated biphenyls (PCB's) in the production, handling, and storage of animal feed.

(a) Polychlorinated biphenyls (PCB's) represent a class of toxic industrial chemicals manufactured and sold under a variety of trade names, including: Aroclor (United States); Phenoclor (France); Colphen (Germany); and Kanaclor (Japan). PCB's are highly stable, heat resistant, and nonflammable chemicals. Industrial uses of PCB's include, or did include in the past, their

use as electrical transformer and capacitor fluids, heat transfer fluids, hydraulic fluids, plasticizers, and in formulations of lubricants, coatings, and inks. Their unique physical and chemical properties and widespread, uncontrolled industrial applications have caused PCB's to be a persistent and ubiquitous contaminant in the environment, causing the contamination of certain foods. In addition, incidents have occurred in which PCB's have directly contaminated animal feeds as a result of industrial accidents (leakage or spillage of PCB fluids from plant equipment). These accidents in turn cause the contamination of food intended for human consumption (meat, milk, and eggs). Investigations by the Food and Drug Administration have revealed that heat exchange fluids for certain pasteurization equipment used in processing animal feed contain PCB's. Although heat exchange fluids in such equipment are considered to be in *closed systems*, leakage has occurred that resulted in direct contamination of animal feed with PCB's and subsequently resulted in the transfer of PCB's to human food produced by animals consuming the contaminated feed. The use of PCB-containing coatings on the inner walls of silos has resulted in the contamination of silage which has in turn caused PCB residues in the milk of dairy cows consuming the contaminated silage. Since PCB's are toxic chemicals, the PCB contamination of food as a result of these and other incidents represent a hazard to public health. It is therefore necessary to place certain restrictions on the industrial uses of PCB's in the production, handling, and storage of animal feed.

(b) The following special provisions are necessary to preclude accidental PCB contamination of animal feed:

(1) Coatings or paints for use on the contact surfaces of feed storage areas may not contain PCB's or any other harmful or deleterious substances likely to contaminate feed.

(2) New equipment or machinery for handling or processing feed in or around an establishment producing animal feed shall not contain PCB's.

(3) On or before Sept. 4, 1973, the management of establishments producing animal feed shall:

(i) Have the heat exchange fluid used in existing equipment or machinery for handling and processing feed sampled and tested to determine whether it contains PCB's, or verify the absence of PCB's in such formulations by other appropriate means. On or before Sept. 4, 1973, any such fluid formulated with PCB's must to the fullest extent possible commensurate with current good manufacturing practices, be replaced with a heat exchange fluid that does not contain PCB's.

(ii) Eliminate to the fullest extent possible commensurate with current good manufacturing practices from the animal feed producing establishment any PCB-containing lubricants for equipment or machinery used for handling or processing animal feed.

(iii) Eliminate to the fullest extent possible commensurate with current good manufacturing practices from the animal feed producing establishment any other PCB-containing materials, whenever there is a reasonable expectation that such materials could cause animal feed to become contaminated with PCB's either as a result of normal use or as a result of accident, breakage, or other mishap.

(iv) The toxicity and other characteristics of fluids selected as PCB replacements must be adequately determined so that the least potentially hazardous replacement should be used. In making this determination with respect to a given fluid, consideration should be given to (*a*) its toxicity; (*b*) the maximum quantity that could be spilled onto a given quantity of food before it would be noticed, taking into account its color and odor; (*c*) possible signaling devices in the equipment to indicate a loss of fluid, etc.; (*d*) and its environmental stability and tendency to survive and be concentrated through the food chain. The judgment as to whether a replacement fluid is sufficiently non-hazardous is to be made on an individual installation and operation basis.

(c) For the purpose of this section, the provisions do not apply to electrical transformers and condensers containing PCB's in sealed containers.

(d) For the purpose of this section, the term *animal feed* includes all articles used for food or drink for animals other than man.

§ 500.46 Hexachlorophene in animal drugs.

(a) The Commissioner of Food and Drugs has determined that there are no adequate data to establish that animal drugs containing hexachlorophene are safe and effective for any animal use other than in topical products for use on non-food-producing animals as part of a product preservative system at a level not to exceed 0.1 percent; that there is no information on the potential risk to humans from exposure to hexachlorophene by persons who apply animal products containing the drug at levels higher than 0.1 percent; and that there is likewise no information on human exposure to animals on which these animal drugs have been used and no information on possible residues of hexachlorophene in edible products of food-producing animals treated with new animal drugs that contain any quantity of hexachlorophene.

(b) Animal drugs containing hexachlorophene for other than preservative use on non-food-producing animals at levels not exceeding 0.1 percent are considered new animal drugs and shall be the subject of new animal drug applications (NADA's).

(c) Any person currently marketing animal drugs that contain hexachlorophene other than as part of a product preservative system for products used on non-food-producing animals at a level not exceeding 0.1 percent shall submit a new animal drug application, supplement an existing application, or reformulate the product by September 29, 1977. Each application or supplemental application shall include adequate data to establish that the animal drug is safe and effective. If the animal drug is currently subject to an approved new animal drug application, each reformulation shall require an approved supplemental application. The interim marketing of these animal drugs may continue until the application has been approved, until it has been determined that the application is not approvable under the provisions of § 514.111 of this chapter, or until an existing approved application has been withdrawn.

(d) After September 29, 1977, animal drugs that contain hexachlorophene other than for preservative use on non-food-producing animals at a level not exceeding 0.1 percent that are introduced into interstate commerce shall be deemed to be adulterated within the meaning of section 501(a)(5) of the act (21 U.S.C. 351(a)(5)) unless such animal drug is the subject of a new animal drug application submitted pursuant to paragraph (c) of this section. Action to withdraw approval of new animal drug applications will be initiated if supplemental new animal drug applications have not been submitted in accordance with this section.

(e) New animal drug applications submitted for animal drugs containing hexachlorophene for use in or on food-producing animals shall include adequate data to assure that edible products from treated animals are safe for human consumption under the labeled conditions of use.

[42 FR 33725, July 1, 1977; 42 FR 37975, July 26, 1977]

§ 500.50 Propylene glycol in or on cat food.

The Food and Drug Administration has determined that propylene glycol in or on cat food is not generally recognized as safe and is a food additive subject to section 409 of the Federal Food, Drug, and Cosmetic Act (the act). The Food and Drug Administration also has determined that this use of propylene glycol is not prior sanctioned.

[61 FR 19544, May 2, 1996]

Subpart C—Animal Drug Labeling Requirements

§ 500.51 Labeling of animal drugs; misbranding.

(a) Among the representations on the label or labeling of an animal drug which will render the drug misbranded are any broad statements suggesting or implying that the drug is not safe and effective for use when used in accordance with labeling direction, or suggesting or implying that the labeling does not contain adequate warnings or